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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/165,522	10/02/98	DAVIS R	10363/005001

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EXAMINER	
RAO, M	
ART UNIT	PAPER NUMBER
1652	

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#16

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/165,522	Davis et al.
Examiner	**Art Unit**
Manjunath N. Rao	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 19, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6 and 18-47* is/are pending in the applica

4a) Of the above, claim(s) *37-40* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 18-36, and 41-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892) ✓

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 1-6, 18-47 are still at issue and are present for examination. Applicants have canceled claims 7-17 and added new claims 18-47. New claims 37-40 drawn to a method of identifying a compound that modulates JNK3-mediated excitotoxicity are patentably distinct from the elected claims because these claims are drawn to identify a compound which modulates a disorder that is mediated by JNK3 and is not related to modulation of the activity (phosphorylation) or the expression of JNK3. Therefore, these claims have been withdrawn from examination by the Examiner as they are not drawn to the elected subject matter. Therefore claims 1-6, 18-36 and 41-47 are now pending in this application.

2. Applicants' arguments filed on 3-19-01, paper No. 15, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 18-36, 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 18-36, 41-47 are directed to methods of identifying compounds corresponding to peptides, peptidomimetics, a small organic molecule or a small inorganic molecules. Claims 1-6, 18-36, 41-47 are rejected under this section of 35 USC 112 because the claims are directed to method of identification of a genus of compounds that have not been disclosed in the specification. No structural description has been provided of all the compounds encompassed by the claims. No information, beyond the mention of the common names such as an organic molecule or an inorganic molecule or a peptide or a peptidomimetic has been provided by applicants which would indicate that they had possession of the claimed genus of compounds. The specification does not contain any disclosure of the structure of all the compounds within the scope of the claimed genus. The genus of compounds claimed is a large variable genus including compounds which can have a wide variety of structures and functions. Therefore many structurally and functionally unrelated compounds are encompassed within the scope of these claims. The specification does not disclose the structure of even a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1-2, 18-19, 23-26 are rejected under 35 U.S.C. 102(e) as being anticipated by McKay et al. (US 5,877,309 dated 3-2-1999, filed on 8-13-1997). This rejection is based upon the public availability of a patent. See previous office action for rejection.

In response to the previous Office action, applicants have traversed the above rejection arguing that McKay et al. disclose the use of only oligonucleotides and that they have now amended the claims to recite peptides, peptidomimetics, small organic molecules or small inorganic molecules none of which are oligonucleotides and as a result McKay et al. does not anticipate amended claim 1 or claim 2 which depends on claim 1. Examiner disagrees. Oligonucleotides are clearly small organic molecules. Furthermore, applicants have not

provided reasons as how oligonucleotides differ from small organic molecules or pointed to any definition of this term in the specification which would exclude oligonucleotides therefrom. In view of the above, McKay et al. continues to anticipate claims 1-2, 18-19, 23-26. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-4, 20, 27-31, 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arco et al. (J. Biol. Chem., 1996, Vol. 271(42):26335) or Lander et al. (J. Biol. Chem., 1996, Vol. 271(33):19705) in view of Gupta et al.(EMBO Journal, 1996, Vol. 15(11):2760-2770) and Nadler et al. (Brain Research, 1980, Vol. 195, 47-56). Claims 3-4, 20, 27-31, 41-47 are drawn to a method of identifying compounds that modulate the activity (phosphorylation of a substrate such as c-Jun) of JNK3 wherein the method comprises incubating the cell that has JNK3 activity with a compound under conditions and time sufficient for the cell to express JNK3 activity, wherein the compound is a peptidomimetic, a small organic molecule or a small inorganic molecule, and comparing the amount of JNK3 activity in the presence and absence of the compound wherein the difference in the level of activity indicates that the compound modulates

JNK3 activity (claim 3-4, 20) or further administering the selected compound to an animal model of excitotoxic disorder and assaying the animal for excitotoxicity, wherein the animal model is a mouse model and the disorder is induced by kainic acid or pentetrazole (claims 27, 31, 41-47).

Arco et al. teach that the structurally unrelated antioxidant agents such as pyrrolidine dithiocarbamate (PDTC), butylated hydroxyanisole (BHA) and N-acetylcysteine (all small organic molecules) activated JNK in Jurkat cells. They also teach the activation of JNK by PDTC and BHA was sustained which correlated with the expression of c-jun. The reference teaches methods to perform the above assay and concludes that JNK is a target of antioxidant agents which can be regulated by oxidant or antioxidant conditions. The reference teaches the assay involving incubation of the Jurkat cell that can express a JNK protein with the antioxidant compounds and measuring the JNK activity by performing in-gel kinase assay of cell extracts obtained from treated and control cells. However, the reference does not teach the different isoforms of the JNK nor does it teach the excitatory experiment involving an animal model.

Lander et al. also teach that NOx (a small inorganic molecule) activates the JNK subgroups of MAP kinases in human Jurkat cells. The reference teaches that JNK proteins were 100 fold more sensitive to NOx stimulation when compared to p38. Furthermore, the reference teaches the effect of NO-generating compounds such as S-nitroso-N-acetylpenicillamine (SNP) and NOx gas on JNK activity (see figure 3) wherein the experiment comprised incubating the Jurkat cells in the presence and absence of the above compounds followed by determination of

kinase activity. (see page 19707). However, the above reference also does not teach the different isoforms of the JNK nor does it teach the excitatory experiment involving an animal model.

Gupta et al. teach the different isoforms of JNK proteins starting from JNK1 to JNK3. Gupta et al. also teach regarding the regulation of JNK protein kinase activity by inflammatory cytokines (small organic molecules or peptides). The reference provides the detailed methods for performing such assays (see the entire document) using substrates such as c-jun and ATF-2 (see page 2766). However, the reference does not teach the use of animal model excitatory experiments.

Nadler et al. teach the Kainic induced neurotoxicity toward hippocampal formation and dependence on specific excitatory pathways. More importantly the reference teaches the extreme sensitivity of rat hippocampal neurons to neurotoxic action of the potent convulsant kainic acid. The reference actually teaches a method of assay of excitotoxic activity of kainic acid and involvement of specific regions of the brain.

Combining the teachings of all the above references it would have been obvious to one of ordinary skill in the art to develop a method of identifying a compound that modulates the activity of JNK3. One of ordinary skill in the art would be motivated to use the newly discovered isoforms of JNK, isolated from the human brain, especially due to the fact that there are 10 isoforms, and develop a method of identifying a compound that would modulate the activity of these isoforms since Arco et al. and Lander et al. already teach methods in which they have identified specific small organic molecules such as PDTC, BHA or NOx which

modulate the activity of JNK proteins. One of ordinary skill in the art would be motivated to develop method to identify compounds as Lander et al. teach that NOx has positive regulatory effects on human peripheral blood mononuclear cells which in turn has now been shown to regulate JNK.

As Gupta et al. show that they have isolated 10 isoforms of the JNK from human brain, one of ordinary skill in the art would be motivated to identify compounds that modulate the activity of the JNK3 in the brain by performing the excitotoxic assay using kainic acid as taught by Nadler et al.

One of ordinary skill in the art would have a reasonable expectation of success since Arco et al. and Lander et al. provide a method wherein they have identified small inorganic/organic molecules which modulate JNK proteins, Gupta et al. teach the existence of several isoforms of JNK and Nadler et al. provide a time tested method of inducing excitotoxic disorder in an animal using Kainic acid.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

8. Claims 5, 21, 22, 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al.(EMBO Journal, 1996, Vol. 15(11):2760-2770) and Nadler et al. (Brain Research, 1980, Vol. 195, 47-56). Claims 5, 21, 22, 32-36 are drawn to a method of identifying compounds that modulate binding of JNK3 to a substrate wherein the method comprises

comparing the amount of JNK3 polypeptide bound to a substrate in the presence and absence of a selected compound, wherein the compound is a peptide, peptidomimetic, a small organic molecule or a small inorganic molecule, wherein the difference in the amount of binding indicates that the selected compound modulates binding (Claims 5, 21, 22) or further administering the selected compound to an animal model of excitotoxic disorder and assaying the animal for excitotoxicity, wherein a decrease in excitotoxicity indicates that the compound modulates the binding, wherein the animal model is a mouse model and the disorder is induced by kainic acid or pentetrazole (claims 32-36).

Gupta et al. teach that JNK protein in general bind to the substrates c-Jun and ATF2 and assay methods to conduct such binding experiments. Gupta et al. also teach the different isoforms of JNK proteins starting from JNK1 to JNK3. The reference however, neither includes assays for compounds that modulate the binding activity nor the excitotoxic method of determination of binding of JNK.

Nadler et al. teach the Kainic induced neurotoxicity toward hippocampal formation and dependence on specific excitatory pathways. More importantly the reference teaches the extreme sensitivity of rat hippocampal neurons to neurotoxic action of the potent convulsant kainic acid. The reference actually teaches a method of assay of excitotoxic activity of kainic acid and involvement of specific regions of the brain.

Combining the teachings the above references it would have been obvious to one of ordinary skill in the art to develop a method of identifying a compound that modulates the

binding of JNK3. One of ordinary skill in the art would be motivated to use the newly discovered isoforms of JNK, isolated from the human brain, especially due to the fact that there are 10 isoforms, and develop a method of identifying a compound that would modulate the binding of these isoforms since Gupta et al. already teach methods for setting up a binding assay of JNK proteins with its substrates such as c-June and ATF-2. One of ordinary skill in the art would be motivated to develop method to identify compounds that modulate binding activity as Gupta et al. teach that JNK regulates the activity of transcription factors in the brain.

As Gupta et al. show that they have isolated 10 isoforms of the JNK from human brain, one of ordinary skill in the art would be motivated to identify compounds that modulate the binding of the JNK3 in the brain by performing the excitotoxic assay using kainic acid induced disorder as taught by Nadler et al.

One of ordinary skill in the art would have a reasonable expectation of success since Gupta et al. teach the existence of several isoforms of JNK as well as a binding assay and Nadler et al. provide a time tested method of inducing excitotoxic disorder in an animal using Kainic acid.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner

by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Manjunath N. Rao
June 4, 2001